

**Title:** Renal safety of bowel preparation with polyethylene glycol for outpatient colonoscopy: an observational prospective study

**Clinical trial registration name and number:** NCT02657564

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## Study Protocol

Colonoscopy has been shown to decrease CRC incidence and mortality by the removal of adenomatous polyps. Bowel cleansing is imperative procedure for colonoscopy examination. Oral sodium phosphate and polyethylene glycol (PEG) are the most frequently used bowel purgatives. Oral sodium phosphate preparations are hyperosmotic and promote colonic evacuation by drawing large volumes of water into the colon (1-1.8 L of water per 45 ml of preparation). Oral sodium phosphate preparations are associated with electrolyte imbalance as well as acute phosphate nephropathy, and the latter could be irreversible, requiring dialysis in some cases. The United States FDA warned that over-the-counter oral sodium phosphate products should not be used for colonoscopy bowel preparation which had led to the manufacturer to withdraw from the United States market.

Currently, polyethylene glycol (PEG) solutions have become the most commonly used preparations for colon cleansing and their renal safety has been shown to be better than that of the sodium phosphate [8,11]. PEGs are non-absorbable isosmotic solutions that pass through the bowel without net absorption or secretion. Significant fluid and electrolyte shifts are therefore attenuated. There is no boxed warning regarding PEG use. PEG preparations can be used in patients with renal function impairment, congestive heart failure, or liver cirrhosis. However, several studies have shown that PEG and oral sodium phosphate share comparable renal safety profile. In addition, one recent population-based study reported that the use of PEG was associated with an increased risk of acute kidney injury (AKI).

The primary aim of this clinical trial is to investigate the incidence and reversibility of AKI among adult patients undergoing colonoscopy with 3-L PEG preparation. The secondary study aim is to evaluate the incidence and severity of electrolyte disturbance with 3-L PEG bowel preparation.

## **METHODS**

### **Patients**

This prospective, investigator-initiated clinical trial will be conducted at Evergreen General Hospital since January 2016. Subjects 40 yrs of age or older scheduled for elective colonoscopy, competent to provide written informed consent, and able to communicate effectively with study personnel are eligible for participation in the study.

Patients are considered ineligible for study participation if any of the following were present: severely reduced kidney function (an estimated glomerular filtration rate [GFR]  $<30$  mL/min/1.73 m<sup>2</sup>); serum electrolyte abnormalities at screening; uncontrolled congestive heart failure (American Heart Association Classification III or IV); unstable angina; untreated dysrhythmia; current use of digitalis preparations or medications known to prolong QT interval; myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery within the previous 3 months; ascites; current acute exacerbation of chronic inflammatory bowel disease; toxic colitis or toxic megacolon; ileus and/or acute obstruction or perforation; ileostomy, right or transverse colostomy, subtotal colectomy with ileosigmoidostomy and/or  $\geq 50\%$  of colon removed; idiopathic pseudo-obstruction; history of gastric stapling or bypass procedure; difficulties swallowing; treatment with an investigational drug or product; participation in a drug study within 30 days prior to receiving study medication; treatment with another bowel preparation within 21 days prior to colonoscopy; known allergy or hypersensitivity to PEG solution; or any other clinically significant disease or finding that, in the opinion of the investigator, would expose the patient to an increased risk of significant adverse event or would interfere with the assessments of the safety during the course of treatment.

## **PEG Preparations and Colonoscopy Sedation**

A split-dose of the bowel preparation with PEG is provided for morning colonoscopy and a same-day preparation is provided for afternoon colonoscopy. Three sachets of PEG dissolved in 3 L of water are used for colon preparation. After completion of PEG ingestion, additional clear liquids are allowed as desired until 2 hours before the schedule time of the colonoscopy. Moderate conscious sedation with fentanyl and midazolam is provided for all endoscopic procedures.

## **Participant Flow and Follow-up**

### *Screening visit (up to 28 days before colonoscopy; Visit 1)*

The following will be obtained or performed at the screening visit: written informed consent, complete medical history, physical examination, vital sign measurements, information regarding concomitant medications received in the past 7 days, information regarding contrast media exposure in the past 3 months, and blood specimen for serum chemistry analysis. A urine pregnancy test will be performed for women of childbearing potential. Patients receive 3 sachets of PEG and are instructed to consume the PEG preparations according to their colonoscopy schedule by study personnel. Each patient is provided with written dietary and PEG instructions.

### *Colonoscopy (Visit 2)*

Immediately before colonoscopy and before each patient is sedated, study staff perform or obtain patient medical history, complete physical examination, vital sign measurements, information regarding concomitant medications received since the screening visit, and specimens for serum chemistry analysis. Patient will complete a questionnaire concerning their experience with PEG on 5-point Likert scale (1 = severely distressing, 2 = distressing, 3 = bothersome, 4 = mild, and 5 = no symptoms). Compliance is assessed by measuring the volume of PEG solution remaining.

Immediately following the colonoscopy, the investigators assign a score for the overall quality of colon cleansing using Boston bowel preparation scale (BBPS). An excellent bowel preparation is defined as a total BBPS score of 8 or higher, a good preparation as a total score of 7, a fair preparation as a total score of 6, and a poor preparation as a total score of 5 or less.

### *Follow-up (up to 28 days after colonoscopy; Visit 3)*

The following will be obtained or performed at the follow-up visit: physical examination, vital sign measurements, information regarding concomitant medications received after colonoscopy, and blood specimen for serum chemistry analysis.

### **Data Analysis and Definition**

The serum creatinine level on visit 1 is recorded as the baseline renal function. Parameters used for assessing the renal function are change in serum creatinine value (differences between visit 2 and visit 3 from baseline serum creatinine levels) and per cent change in creatinine value (the percentage change of serum creatinine compared to baseline value). AKI is defined as  $\geq 50\%$  increase in baseline serum creatinine. The proportion of patients with  $\geq 25\%$  increase above their baseline creatinine level will also be identified. In addition, We will compare the change in the estimated GFR (differences between visit 2 and visit 3 from baseline GFR value). The GFR is estimated using the Modification of Diet in Renal Disease Study Group (MDRD) formula. Assessment of changes in serum electrolyte values (including calcium, phosphate, chloride, magnesium, sodium, potassium) between visit 2 and visit 3 from baseline values are also performed. The incidences of electrolyte disturbance will be evaluated.